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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,473	03/01/2002	Melissa K. Carpenter	090/003C	1663

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EXAMINER

TON, THAIAN N

ART UNIT PAPER NUMBER

1632

DATE MAILED: 07/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/087,473	Applicant(s) CARPENTER ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 April 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-6,9-11,17,18 and 29-32 is/are pending in the application.
- 4a) Of the above claim(s) 29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-6,9-11,17,18 and 30-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Applicants' Amendment and Response, filed 4/18/05, has been entered. Claims 7-8, 13-15, 23-28 are cancelled. Claim 29 is withdrawn. Claims 1-2, 4-6, 9-11, 17-18, 30-32 are under current examination.

Claim 29 is withdrawn, as stated in the prior Office action. Newly submitted claim 29 is directed to an invention that is independent or distinct from the elected invention for the following reasons: the claim is found to correspond to Group II of the Restriction Requirement, mailed 3/19/04. Since applicant has received an action on the merits for the Group I, claim 29 is withdrawn from consideration as being directed to a non-elected invention.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See p. 19, line 4.

Double Patenting

The prior rejection of claims 1, 2, 7, 12-17, 19, 20 as being provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6-8, 12, 13 of copending Application No.

09/994,440 is withdrawn because the '440 claims do not recite producing a population of cells containing 2% that express tyrosine hydroxylase.

Claim Rejections - 35 USC § 112

The prior rejection of the claim 1, 2, 4-11, 13-15, 17-18 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn, as the claims no longer recite a population of cells that is "at least 75% homogenous for a particular cell type".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-6, 9-11, 17-18, 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". This is a new matter rejection.

The amendment introduces new matter into the disclosure with the recitation of harvesting a population of neural cells, wherein at least 2% of the cells express tyrosine hydroxylase. Careful review of the specification fails to provide specific description and support for this amendment. In particular, the specification teaches the generation of differentiated cells using various treatments, and states that, about 5-12% of the cells are neurons, based upon morphology and β -tubulin-III staining, and about 1/3 of these are mature neurons. Further, the specification teaches that 2-5% of total neurons (5-15% MAP-2 positive neurons) also stained for tyrosine hydroxylase. The claims state the harvesting step of "neural cells". The specification only supports, at the very most, neurons. "Neural cells" encompasses various cell types, for example, neurons, glial cells, etc. There is no specific description in the specification to support the instant amendment. Furthermore, it appears that of the 5-12% of neurons, only 2-5% of these neurons stain positive for tyrosine hydroxylase. Thus, this gives a much smaller amount than the "at least 2%" that is instantly claimed.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1-2, 4-6, 9-11, 17-18, 30-32 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. (Emphasis added).

Claims 1-2, 4-6, 9-11, 17-18, 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection, necessitated by Applicants' amendments to the claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)).

These include: nature of the invention, breadth of the claims, guidance of the

specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The claims, as currently amended, recite methods for producing a cell population containing 2% that express tyrosine hydroxylase by providing a suspension of undifferentiated hES cells that are free of feeder cells; plating and culturing the suspended cells on a solid surface so that they differentiate without forming embryoid bodies; culturing the plated cells in a medium containing a TGF-beta superfamily antagonist; and harvesting a population of neural cells from the solid surface, wherein at least 2% of the cells express tyrosine hydroxylase (TH).

The claims are not enabling for the following reasons: as stated in the prior Office action, the claims require that the hES cells are grown in conditions that are free of feeder cells. However, the claims are not enabling for this breadth, as established in the prior Office action, culturing of hES cells require factors that are generally provided for by the fibroblast feeder layers. However, in the absence of these feeder cells, the hES cells will either differentiate or die. See Thomson (cited previously). Thus, in order to maintain undifferentiated hES cells, as evidenced by the working examples in the specification, extracellular matrix must be provided. See Example 1. The state of the art supports the unpredictability in culture hES cells, as evidenced by Lim (cited previously) who show that the components that

fibroblast feeder cells provide to maintain hES in an undifferentiated state, are yet uncharacterized. Accordingly, in view of the unpredictable state of the art for maintaining undifferentiated hES cells, the instant specification is found to be enabling only with regard to culturing hES cells under feeder-free conditions in the presence of an extracellular matrix and fibroblast conditioned medium.

The claims, as now amended require the production of a population of cells containing at least 2% that express TH. Specific embodiments teach culturing the hES cells in a medium containing specific TGF-beta superfamily antagonist to differentiate the hES cells (for example, BDNF, NT-3, noggin, or follistatin). Further embodiments claim that the differentiated cells are identified as neural cells, wherein at least 50% of the cells express polysialylated NCAM, at least 50% of the cells express β -tubulin III, and at least 10% of the cells express MAP-2.

The specification is not enabling for the breadth of these claims. Example 5 teaches directed differentiation of hES cells to neurons. Note that the claims are broadly directed to "neural cells", which encompass other cell types, other than neurons. In particular, the working example provides various test factor groups, which provides a complex mixture of factors, and then the differentiated cells are identified from these various conditions. In particular, Groups 4-5 are TGF- β superfamily factors, which specifically recite BMP-2, GDF-5, GDNF, Neurturin, noggin, and follistatin. See Table 3. Table 4 provides the results from these experiments, and it is noted that only those treatments which contain Test Group 5

(i.e., noggin and follistatin) are able to produce any cells with TH positive staining. See Treatments B, D, and F. Treatments A, C, E, G have Test Group 4, which contain other TGF- β superfamily factors, which are unable to provide any noticeable percentage of TH positive cells. Thus, the specification is only enabling for producing TH positive cells when utilizing noggin or follistatin. There is no teaching, guidance, or evidence of record to show that utilizing any other TGF- β superfamily factors (such as those recited in Test Group 4), would result in the production of at least 2% TH positive cells, as required by the claims. Furthermore, it is noted that even these test groups fail to provide more than 0.5% TH positive cells, thus, the instant specification fails to enable the claimed invention. Finally, with regard to Table 5, it is noted that Treatment D results in 15% of MAP-2 cells positive for TH. There is no guidance with regard to how many percent of cells are MAP-2 positive from Table 5. The specification, upon describing Figure 4 states that 2-5% of total neurons (5-15% of MAP-2 positive neurons) are also TH positive (see p. 35, lines 9-13). This does not correspond to the instantly claimed embodiment of at least 2% TH positive, as only 2-5% of 5-15% is not within the scope of the claims.

One of skill in the art, given the teachings in the specification would not be able to rely upon the state of the art of directing differentiation of hES cells to neural cells, as evidenced by the cited art of record in the prior Office action. Du (cited previously) show the unpredictability in the art with regard to directing

differentiation to a particular cell type from an undifferentiated ES cell. The specification fails to overcome these unpredictabilities, and thus, the claimed invention is not found to be enabling.

Accordingly, in view of the lack of teaching or guidance provided by the specification with regard to the production of cells wherein at least 2% express TH, using the claimed methods, the breadth of the claims, with regard to the specific factor(s) that would be used to differentiate the cells, the unpredictable state of the art of directed differentiation of hES cells, the lack of specific guidance with regard to specific factors and morphogens to produce the claimed cell population, it would have required undue experimentation for one of skill in the art to practice the claimed methods.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. U.S. Pat. No. 6,833,269 (Carpenter *et al*) discusses making neural cells by culturing embryonic stem cells. However, they do not anticipate or make obvious the claimed invention because they do not contemplate these methodologies without the formation of embryoid bodies.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Art Unit: 1632

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt

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